EFFICACY OF PUVA THERAPY IN VARIOUS TYPES OF VITILIGO

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CERTIFICATE

This is to certify that the dissertation entitled "**EFFICACY OF PUVA THERAPY IN VARIOUS TYPES OF VITILIGO"** is the bonafide original work of **Dr. K. MEENAKSHI,** in partial fulfillment of the requirements for **M.D. (Dermatology, Venereology and Leprology) BRANCH – XII** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in March 2007. The period of study was from February 2005 to March 2006.

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DECLARATION

I, **Dr. K. MEENAKSHI,** solemnly declare that dissertation titled, "**EFFICACY OF PUVA THERAPY IN VARIOUS TYPES OF VITILIGO"** is a bonafide work done by me at Govt. Stanley Medical College & Hospital during 2004-2007 under the guidance and supervision of **Dr. A.M. JAYARAAMAN, M.D., D.D.,** Professor and Head, Department of Dermatology, Stanley Medical College, Chennai-600 001.

The dissertation is submitted to Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (BRANCH – XII) in Dermatology, Venereology and Leprology.**

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Date :

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The trend in medical care is toward personalized and predictive therapeutics. Individual variation in responsiveness and toxicity is increasingly recognized. We are on the edge of a revolution in health care.

We expect that many of the new treatments will be increasingly used in a cost effective manner. The arrival of photochemotherapy had revolutionized the treatment for vitiligo.

I thank **Dr. D.R. GUNASEKARAN, M.S., FICS.,** Dean, Govt. Stanley Hospital for permitting me to conduct the study.

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CONTENTS

INTRODUCTION

Vitiligo is an acquired common pigmentary disorder clinically characterized by the development of depigmented macules which are caused by the destruction of melanocytes in the affected areas . This is described in the Hindu sacred book ATTARVA VEDA in 1400 B.C. This had been often confused with leprosy .This misconception among the people is the basis for the social stigma tagged with this disease. In certain culture, patients with vitiligo are still regarded as social outcasts.

About 0.5 – 1 % of general population suffer from vitiligo. Half of all the patients develop the disease before the age of twenty. Onset at an old age occurs but is unusual and should raise concern about underlying disorders or associated diseases[52].

Generalized vitiligo is the most common clinical presentation and commonly involves the face and acral area. Vitiligo is not a life threatening disease and does not require treatment unless severe cosmetic disfigurement causes emotional and social distress[9].

Most often, depigmentation is gradually progressive process but in generalized vitiligo , patients may report a sudden onset with rapid spread of vitiligo over a period of few months . Subsequently the disease

may remain quiescent for many years. Upto thirty percent of the patients report “spontaneous” repigmentation, which appears in perifollicular and marginal areas of sun exposed lesions during the summer months. Complete sunlight induced repigmentation is extremely rare. Independently of the initial course of the disease, vitiligo may come to a halt and remain stable for decades. Focal and segmental vitiligo usually do not extend beyond their initial regional distribution, and once the expansion stops, they tend to be quite stable .Segmental vitiligo can also occur as a distinctive part of generalized disease and may precede its onset[10]. At present there is no universally effective drug for vitiligo therapy. The various treatment modalities include steroids (topical and systemic), cyclophosphamide pulse, and clofazamine , placentrex (topical and injection) , autologous melanocyte transplant, choloroquine, Khellin – UVA(KUVA), PAUVA (Lphenylalanine + UVA), fluorouracil (topical), tacrolimus induce temporary clearance with recurrence after variable intervals[14,41].

Of several therapeutic options available one of the promising therapies is PUVA (Psoralen and UVA). This is based on the observation that in many patients sun exposed lesions tend to show follicular repigmentation during the summer months.

With the increased sensitivity of vitiligo to sun burn and the unpredictable dosimetry with natural sunlight, solar phototherapy as not evolved into a true therapeutic option. On the other hand, first description of vitiligo treatment with what can be considered photo chemotherapy dated back about 4000 years which makes PUVA one of the oldest therapeutic principles that are still in use in the 21st century.

Heliotherapy (sunlight therapy) was first introduced by Herodotus; a renowned Greek physician of the 2nd century B.C has been called the Father of Heliotherapy[7].

Indians used the tropical plant extract (Psoralea corylifolia) combined with subsequent sun exposure as early as 1400 B.C. Later around 12th century A.D., the Egyptians used Psoralen obtained from another plant Ammi majus[7].

Photo chemotherapy of vitiligo was revived for modern medicine of a century ago when El Mofty published the success of his therapeutic trial and subsequently identified the Psoralen as the active compound.

Kelly and Pinkus reported some success in treating vitiligo with oral administration of 8-MOP followed by sunlight exposure. Since natural sunlight lacks predictability often changing emission spectrum,

changing its output as day progresses, in 1960 it was realized that 8-MOP optimally sensitizes the vitiliginous skin at 360 nm., the UV light box was born[7].

In 1974 Parrish et al successfully treated generalized Psoriasis with oral 8-MOP and high intensity UVA therapy and coined the term (acronym), PUVA[8].

AIM

1) To evaluate the efficacy of therapeutic effect of oral psoralen followed by Ultraviolet - A irradiation (PUVA) for chronic vitiligo patients who failed to respond to other modalities of treatment for vitiligo

2) To assess the efficacy of PUVA response at various sites involved.

3) To study the Age, Sex, Family History, Koebnerization, surface area of involvement and their influence on the PUVA response.

4) To study the association between blood group and its efficacy on PUVA therapy.

5) To assess the complication due to PUVA therapy.

REVIEW OF LITERATURE

HISTORICAL ASPECTS

The word vitiligo might have evolved from the Latin word "vitium" meaning a defect / blemish. Vitelius signifying a calf's white patches. Documentation of the use of the word vitiligo occurred in the first century A.D. by the Roman physician 'Celus'.

Indian literature dating to 1500 to 1000 B.C. refers to the word "kilas" ('kil' means white, 'as' means to caste) .Palita ('pal' implies grey, old and aged) referring to white patches on the skin. In the sacred book of Buddhism 'Vinay Pitak' (621-544 B.C) , persons suffering from kilas were unable to be ordained[63].

EPIDEMIOLOGY

Vitiligo occurs all over the world and in all races, it accounts for about 0.5 –1% of general population[59]. In India the incidence is as high as 8.8%[3]. Family history is noticed in 20-30% of cases[59]. Inheritance is thought to be polygenic or autosomal dominant with incomplete penetrance and variable expression[59]. It is more in monozygotic twins than in dizygotic twins. Incidence in Caucasians is 1%. Both sexes are

equally affected. Vitiligo may develop at any age and onset has been reported from birth to 81 years of age. The peak age of onset is between 10 –30 years. Half of them manifest before 20 years[28]. Segmental vitiligo appears notably familial[53]. HLA DR A1 , 0302 , HLA DQ A1, 0601, DQ B1 ,0803 , DR B1-0503 alleles predispose individuals to vitiligo and HLA DR A1 6501 alleles protect individuals from vitiligo[60]. HLA B13 is associated with vitiligo and antithyroid antibodies[62].

AETIOLOGY

The exact aetiology is unknown. So various theories are proposed namely,

1. Autoimmune theory.
2. Neural hypothesis.
3. Self destruction hypothesis.
4. Other prevailing hypothesis.

AUTOIMMUNE THEORY

In vitiligo autoantibodies are directed against various melanocytic proteins including tyrosinase related proteins 1, 2 which correlate with

the disease activity. In progressive vitiligo increased levels of CLA, active CD8 + T cell in the peripheral blood of the patient[28].

Several autoimmune diseases have been associated with vitiligo such as Hypothyroidism[16], Hashimoto's thyroiditis (20-30%)[44], pernicious anaemia[52] (4-20%), Addisons disease[37] hypogonadism[44], halonaevus, scleroderma, lichen planus, DLE, rheumatoid arthritis, alopecia areata[3].

Vitiligo is more often associated with late onset diabetes mellitus[56]. Diabetes mellitus both juvenile onset and adult onset types occurs in 1- 7.1% of vitiligo patients and conversely vitiligo occurs in 4.8% of diabetic patients[28].

Autoimmune poly endocrinopathy, candidiasis, ectodermal dystrophy (APECED) with gene mutation in AIRE (autoimmune regulator) has been increasingly associated with vitiligo[52]. The presence of an auto immune reaction of uveal tract along with the meningeal, cochlear epidermal melanin in Vogt-Koyanaki-Harada Syndrome leading to destruction of melanin support the role of immune response in vitiligo[49].

A non-cytotoxic antikeratinocyte intracellular bodies directed against 40 KD or 75 KD common tissue antigens and 65 KD and 90 KD pigment cell specific antigens correlate with the disease activity and more pronounced in active rather than stable vitiligo[63].

In Neural Hypothesis, increased immune reactivity of neuropeptide Y/ altered balance of nerve growth factor receptors lead to increased expression of catechol –o-ethyl transferase and mono amino oxidase and Beta 2 adreno receptors[28].

Studies has shown that disturbance of the autonomous nervous system leading to depigmentation may lead to vaso constriction.

1. Clinical evidence of segmental and dermatomal vitiligo.

2. Increased sweating and vaso constriction in vitiliginous areas implies increased adrenergic activity.

3. Elevated levels of tumour necrosis factor α (TNFα), intercellular adhesion molecule –1 (ICAM 1) and Interferon γ have been found in perilesional skin in the vitiligo patients[64].

Degenerative and regenerative changes were found in the terminal regions of the small proportion of the nerve supplying central

and marginal regions of vitiliginous lesions indicating that affected nerves were auto immune in function[6].

SELF DESTRUCTION HYPOTHESIS:

A.B. Lerner states that loss of intrinsic protective mechanism that eliminate toxic intermediate metabolite in the melanocytic pathways leads to the accumulation of 5,6,7,8, tetrahydrobiopterin which increase the production of hydrogen peroxide[28].

OTHER PREVAILING HYPOTHESIS:

1) Intrinsic defect of structure and function of rough endoplasmic reticulum in vitiligo melanocytes.

2) Deficiency in melanocyte growth factor.

3) Dysregulation of melanocyte apoptosis.

4) Primary disturbance in T cell resulting in the development of forbidden clones of auto reactive lymphocytes in the epidermis[28].

In Vitiligo, onset of the activity often attributes to emotional stress which causes increased release of catecholamines from nerve endings[19].

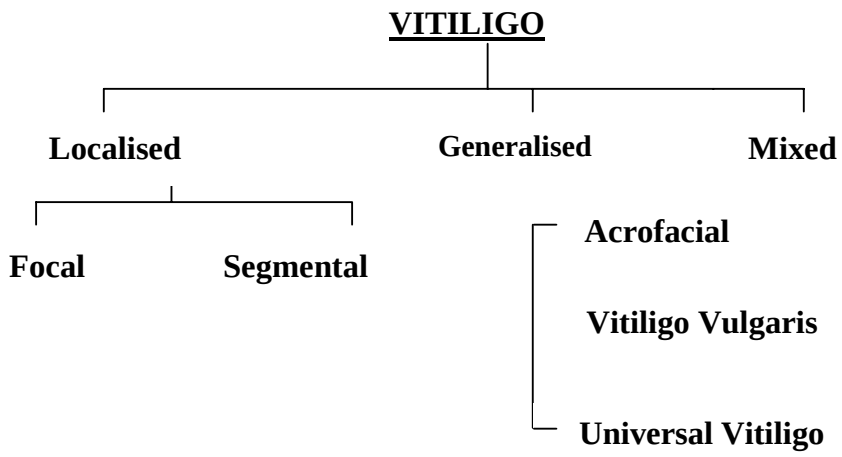
Studies have shown that reduced zinc level significantly correlates with vitiligenous lesion[61].

Lower level of catalase and UV induced damage to the epidermis release free reactive oxygen species which are cytotoxic to melanocytes and also inhibit tyrosinase[32].

Emotional factors, physical injury, sunburn are often associated with the onset of the disease[19].

Spontaneous repigmentation was due to the release of cytokine from the donor site when stimulating the vitiliginous patch and hair follicle of the grafted site[65].

CLASSIFICATION OF VITILIGO (after Fitzpatrick 1987)[58,29]:



1. LOCALISED:

Focal –one or more patches, non dermatomal distribution

Segmental –one or more patches in dermatomal distribution.

2. GENERALISED

a. Acrofacial – Acral (hands and feet)

Orificial (around mouth and genitals, eyes, nose and ears)

Lip tip (Acral, nipple, genital, lips)

b. Vulgaris - Scattered patches in symmetrical or asymmetrical distribution

c. Universal - Total or near total.

2. Mixed -

Segmental with acro-orificial or vulgaris

Trichrome vitiligo –

Uniform, narrow, hypopigmented zone between normally pigmented skin and the typical vitiligo macules [51].

A trichrome lesion naturally evolves to a typical white vitiligo macule or macules albeit not at a predictable rate. Trichrome vitiligo occurred mostly on the trunk in active vitiligo vulgaris[28]. Focal vacuolar degeneration of the basal cell layer and mild inflammatory cell infiltrate of epidermis and dermis were prominent in the light brown skin and perilesional normal skin than in other normal area of the skin. Decreased number of melanocytes in the tanned skin compared with vitiliginous skin is observed[24].

1. Quadrichrome Vitiligo :

It refers to the fourth colour. This is a marginal hyper-pigmentation in addition to trichrome vitiligo.

2. Pentachrome Vitiligo :

It has white, tan, brown hyperpigmented, blue grey hyper-pigmented and normal colour.

3. Blur Vitiligo :

This corresponds to vitiligo macules occurring in the sites of post inflammatory hyper melanosis.

4. Inflammatory Vitiligo :

This has an erythematous raised border similar to that seen in tine a versicolor.

5. Confetti Macules :

This is seen as multiple vitiliginous macules of 1-2 mm diameter[28].

PSORALEN PHOTO-CHEMOTHERAPY

Psoralen photo – chemotherapy is by which psoralen and UVA are used to bring beneficial responses to patients suffering form vitiligo. Such beneficial responses are not produced by the drug or radiation alone[2].

HISTORICAL BACKGROUND

Psoralen and its derivatives are naturally occurring tricyclic furo coumarins found in more than thirty plants such as lime, lemon, bergamot, fig cloves, and babache[2].

The ancient Egyptians and Indians used plant extracts and applied to the skin or administered orally in combination with sunlight to

produce photo toxicity in vitiliginous skin with subsequent repigmentation in 1400 B.C[7].

The most widely used plant derivatives in photo – chemotherapy are 8-MOP produced by the plant Ammmi Majus, Ficus carica. 5 MOP is also known as Bergapten, majudin and Heraclin. This is also produced by citrus and psoralea corylifolia. These psoralen are present in the leaves, fruits, seeds, roots, and the rhizome of the plants[3].

In 1940 – Isolation of psoralen from Ammi Majus was done[7].

In 1947 – El Mofti et al showed the psoralen's therapeutic efficacy in vitiligo[2].

In 1950- Both topical and oral psoralen was used in vitiligo[7].

In 1954- a Pharmacologic study of psoralen by Pathak and Fitzpatrick in the Unites States and by Musajo and his collaborators in Italy was done[18].

In 1960- Synthetic furo coumarin trimethyl psoralen was used in the treatment of vitiligo[18].

In 1974- Artificial UVA after oral administration of 8 MOP in psoriasis was called acronym PUVA by Parrish et al[2].

In 1988 – NUVB was discovered by Van Waden et al and Green et.al.

In 1997 – Westerhof and Nieweborers first used NBUVBin Vitiligo[66].

TYPES OF PSORALEN AVAILABLE ARE:

1) Natural – 8 Methoxy psoralen (8 MOP)
   5 Methoxy psoralen (5 MOP)[3].
2) Synthetic – 4,5,8, Trimethyl psoralen
   3 carbethoxy psoralen (3 CP)[21]

8 Methoxy Psoralen (8MOP)

It has molecular weight of 216 .2 and occurs as a white to cream coloured, odourless solid that forms needle like crystals. It is soluble in acetone, acetic acid, propylene glycol and benzene. It is sensitive to air and light and is easily hydrolysed. Its melting point is 148 ° C. Psoralens are lipophilic, non ionized compounds, very poorly soluble in water and ether[20].

This poor solubility impedes their absorption from the stomach and the intestine. A micronized crystal in gelatin capsules is more rapidly and completely absorbed. Fasting condition increase psoralen absorption. Fatty meal decreases its absorption and delays its peak level.

Medication should be taken with water only. Ideally food should be avoided until after the treatment[70].

High level of psoralen in blood under fasting condition can cause nausea which can be alleviated by taking along with food or milk[18].

After absorption psoralen exhibits peak serum level between 1 and 6 hours[2]. It also exhibits strong but saturable first pass effect through the intestines and the liver[70]. 75-85% of methoxalen is reversible, bound to serum albumin and 98-99% in case of 5 MOP (5 Methoxypsoralen) Epidermal cell binding is about 90% in case of 8 - MOP, 79% in case of 5- MOP studies have shows that psoralen spreads rapidly to most organs but binding seems to be short lived and reversible, provided that there is no exposure to UVA irradiation[70].

8-MOP is completely metabolized in the liver and oral 8-MOPhas serum half life approximately 1 hr and it is rapidly eliminated. There appears to be no accumulation of metabolites. Hence repeated dose does not cause significant accumulation of the drug in the body. After ingestion of psoralen, the skin is most sensitive to UVA after 1-3 hours but remain active upto 8-12 hours[2].

The drug is completely excreted in 12hours (80% in 6-8 hours and 90% in 12hours)[2]

The unpredictable pharmaco kinetic behaviour is probably due to large inter individual and small intra individual variation in absorption and bio availability[12]. Eventhough psoralen appears to be distributed to all cell organs, photochemical binding occurs only in the skin , eye and blood[71].

8-MOP is taken orally as a capsule in a dose of 0.6 to 0.8 mg/ kg bodyweight, one to two hours before exposure to UVA radiation[3].

In general, 0.4 mg /kg bodyweight is recommended because of more predictable absorption, lower incidence of nausea and one hour interval is more convenient for patient and cost saving[70].

The liquid methoxalen formulation provides more rapid, higher and more reproducible peak serum level than crystalline formulation[18]. Tolbutamide displaces 8-MOP from its binding site and enhance photosensitivity[2].

MECHANISM OF PSORALEN'S ACTION

Photo activated psoralen is mostly confined to skin and eye, thus PUVA represents a form of target related chemotherapy. The exact mechanism by which photo sensitivity occurs following PUVA is not precisely known. The absorption of psoralen maxima lie in 210- 310 nm. The action spectrum for oral PUVA is probably in the range of 320-325 nm. In psoralen treated skin, on exposure to UVA rays, two distinct reactions take place[7].

TYPE 1 –ANOXIC REACTION

The site of cellular damage is primarily the DNA of the cell nuclei by forming mono functional and bi functional adduct in the DNA of melanocytes, there by increasing G2 phase of the cell cycle in which Melanocyte Stimulating Hormone (MSH) receptors are more active[33,18].

TYPE 2

It is oxygen dependent and forms free radicals .In this type, reactive form of the psoralen in its triplet state and the site of these reactions are DNA, chromatin, cell membrane of epidermis, dermal endothelial cell, cytoplasmic constituents of melanocytes which cause

release of IL-1 and facilitate the binding of keratinocytes to more α MSH receptors[7].

Amelanotic melanocyte in hair follicle was discovered by Staricco in 1959. The mechanism by which melanocytes repigment was further elucidated by Orfonne et al and Cui et al[63].

PUVA causes repigmentation by activation of the inactive melanocytes in the middle and the lower part of hair follicle and hair root sheath. Inactive melanocyte contains only structural melanosomal protein but don't contain enzymes required for melanogenesis[63].

PUVA suppresses number of functional blood peripheral lymphocytes, polymorphic mononuclear lymphocytes, macrophages and T cell, diminished mitogen response showing beneficial effect within immune reaction by reducing Langerhan cells 6 to 7 days after PUVA and change in number and morphology of above cells and return to normal by 14 days after stopping PUVA[2].

El Mofty proposed the mechanism by which psoralen induces pigmentation.

1) Release of inhibited tyrosinase enzyme[31].

2) Induction of migration of active melanocytes from the surrounding normal epidermis and hair follicle by inflammatory mediators such as Leukotriene C4 (LTC4), Leukotriene D4 (LTD4) , TGF α, melanocyte growth stimulating factor which are released by keratinocytes secondary to UV damage[7].

3) Increased tolerance to UVR / solar exposure and thereby stronger stimulation of melanocytes[7].

4) Correction of abnormalities of structure of melanocyte in vitiliginous skin[7].

5) Reactivation of inactive melanocytes in vitiliginous patch[7].

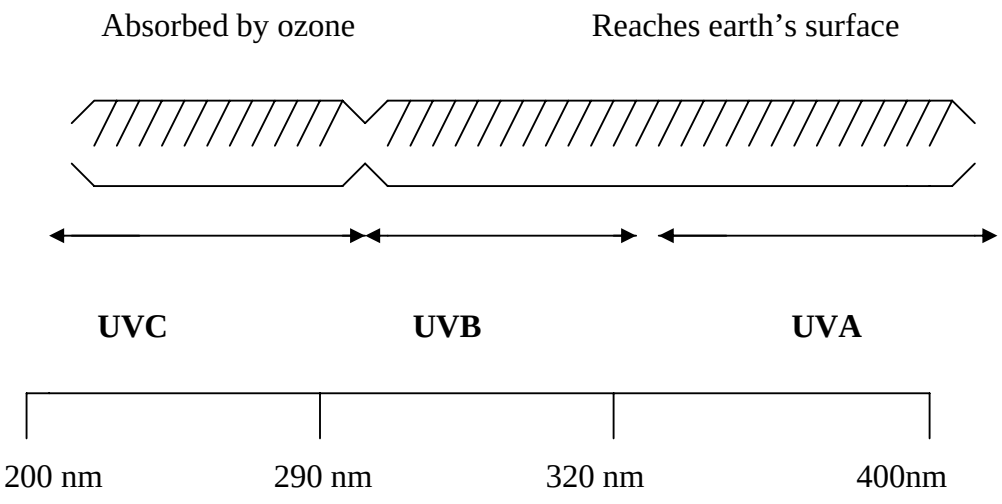
PUVA increases denova expression of SA beta galactosidase, a marker of fibroblast senescence in vitro and vivo which result in 5 to 8 fold upregulation of matrix metaloproteinase I, III and result in premature aging[26].

UVA exposed kertinocytes express 2 factors (P-1, P-2),. with molecular weight 20KDa, 1 KDa respectively. Its stimulates DNA synthesis in human keratinocytes by expression of cytokines like IL6, IL8, Granulocytes / macrophages colony stimulating factor[11].

PUVA treatment may deplete vitiligo associated melanocytic antigen (VAMA)[68]. PUVA inhibits 'S' phase of cell cycle[57].

ULTRA -VIOLET RADIATION

Ultra violet radiation is a part of spectrum of electro magnetic radiation. Wave length less than 290 nm are absorbed by ozone layer which is about 25- 30 km above the earth's surface. The wave length less than 260 nm are absorbed by cellular protein and wave length of 280nm are absorbed by cellular nucleic acid , causing cell damage and cell mutation[45].



CHARACTERISTICS OF UV AND VISIBLE LIGHT [35]

Light	% of solar Radiation reaches earth	Wave Depth (nm)	Window glass peneterance	Erythrogenecity	Carcino genecity	Delayed tanning	Depth of the Peneterance
UVA	0	200-290	--	++ +	+++	--	Epidermis
UVB	1.7	290-320	--	++	++	++	Epidermis + Papillary dermis
UVC	6.3	320-400	+	+	+	+	Papillary + reticular dermis
Visible	9.2	400-800	+	--	--	+	Reticular dermis + subcutaneous Fat

Maximum UVL reaches the earth at noon because of the transverse passage of rays. More UVL reaches the earth in summer[50]. Solar radiation that reaches the earth is either reflected, transmitted or attenuated by gas molecules and water droplets at 330 nm, by stratospheric ozone absorption between 200 to 330 nm and by oxygen below 200nm[27].

UV rays are reflected by snow (85%), sand (25%), dribbling water (5%), decreased by cloud 20-90%, 60% by every 50 cm traveled through water[27].

UVC is totally filtered by atmospheric ozone and is not present in sunlight. It can be artificially produced by the use of filters. Artificial

source of UVC is cold quartz. They are inexpensive, do not need time to warm up or cool off. UVC is mutagenic in vitro, effectively killing micro organisms in the immediate vicinity. It is used for sterilizing environment in the operating rooms. Desquamating effect of UVC have been used to treat acne patients. UVC does not promote skin pigmentation, but it does cause an immediate burning sensation and desquamation 24 to 48 hours after treatment. It has the highest energy part of the UV radiation[38,27].

UVB (290-320nm)

It is referred to as sunburn spectrum because exposure to this causes sunburn and delayed tanning. In addition, certain individuals react abnormally to solar radiations such as urticarial papules, vesicles, plaque etc[33].

UVA (320-400nm)

It causes depletion of antigen presenting cell and induces transient and less effective immune suppression. UVA rays can penetrate the skin deeply upto subcutis and trigger the production of melanin causing immediate tanning and premature ageing, stratum corneum thickening and epidermal hyperplasia[55]. On earths surface the

ratio of UVA to UVB 20:1[27]. UVA is strongest between 10 A.M. and 4 P.M. This is not absorbed by unstained glass and has the lowest energy of UV radiation[38]. UVA increases skin temperature to cause pain at 42° C and immediate pigmentation between 6 and 20 j/sq. cm[23]. UVA is sub-divided into UVA 1 (340-400nm) and UVA 2 (320-340nm). Biologically speaking, UVA 2 is more effective than UVB[27].

The psoralen photo chemotherapy action spectrum is UVA portion of eletro magnetic spectrum.

PHOTOTHERAPY UNITS

PRINCIPLES OF PHOTOTHERAPY :

UV radiation is produced artificially by the passage of electric current through a gas, usually vaporized mercury. The mercury atoms become excited by the collision of electrons flowing between the lamp's electrodes. The excited electrons return to the particular electronic state in the mercury atom and in doing so they release some of the energy that they had absorbed in the form of optical radiation which is called as UV rays[45].

All bodies whose temperature is above absolute zero (Kelvin = -273 °c) emit electro magnetic radiation. The higher the temperature, the more intense becomes the radiation and the greater becomes the short wavelength radiation components. With rising temperatures, the short wavelength ranges increase more strongly, and the longer wavelength ranges less strongly than the total radiation.

The Stefen- Boltzmann law states that the total electro magnetic radiation of a body varies with the fourth power of the temperature. In this case, the total radiation signifies the wavelength range between zero and infinity.

TYPES OF PHOTOTHERAPY UNITS AVAILABLE:

1) Conventional incandescent lamps
2) Halogen incandescent lamps
3) Discharge lamps
4) Low pressure mercury vapour lamps
5) High pressure mercury vapour lamps
6) Metal vapour halogen lamps
7) Short arc mercury vapour lamps (maximum pressure lamps)
8) Xenon short arc lamps.
9) Fluorescent lamps

DISCHARGE LAMPS :

In this the radiation is generated when current flows through gases or metal vapors. The non conductive gas to a conductive state is done by means of high voltages which are briefly applied and are generated by specially designed starters or ignition systems. There are used for cosmetic and therapeutic applications and are intended to generate UV and short wavelength IR radiations simultaneously. The source for the UV radiation is a mercury high pressure arc tube. IR radiation is generated by a tungsten coil .This coil also performs the

function of ballast resistance too. Discharge lamps are supplied in many size and designs.

1) Low pressure mercury lamps
2) High pressure mercury lamps
3) Low pressure sodium lamps
4) High pressure sodium lamps
5) Metal vapour lamps
6) High pressure xenon lamps
7) High pressure krypton lamps

LOW PRESSURE FLUORESCENT LAMPS

Lamps emit radiation within UVA 350 and 370 nm.

PROPERTIES

Power levels, compact lamps	7-18 W
Power level, tubes	40-100 W
Lamp lengths, compact lamps	14 – 24 cm
Lamp lengths, tubes	60-180 cm
Supply voltage	125 – 230 V
Operations	Using chokes and starters or using electronic adapter systems. All systems

	must be approved for the respective type of lamp,
Brand Designation	Light colors 78 and 79, Eversun Super, TL / 10,12, TL/09, CLEO.

INFLUENCES THAT CAN CHANGE THE RADIATION OF A LAMP:

Depending on the time, temperature, mechanical and electrical adjustments, variations of the lamp emissions can result. Sometimes also the bulb material will change without consequences in the visible range, but it is possible that by this constructive variation, the UV radiation will be changed. Some of these influences can ameliorate. For example, by prolongation of the irradiation time or by better cooling[40].

In this study, high pressure mercury vapour half body and hand and foot lamps were used in the phototherapy units. These are compact lamps. It contains mercury. This type of lamp is relatively economical as a long service life of many thousands of hours and is used widely nowadays in the treatment of psoriasis and vitiligo. The bulbs have 125 – 1000 watts power[45].

The spectral emission from this type of units is from 254 nm - 366nm peak 352 nm and emit approximately 0.5 % of UVB. High

pressure mercury lamps are manufactured at the power level of 125 watt, with a so called black glass bulb which absorbs the visible lines and transmits only the UVA line at 366nm[40,25].

Regular broad band UVA lamps, which are manufactured for PUVA therapy, serve as light sources for the photo chemotherapy for vitiligo. These are either fluorescent lamp bulbs or metal halide lamps. If metal halide lamps are use, a UVB filter is required to eliminate the shorter wavelength portion of the emission spectrum.

DOSIMETRY:

The radiation energy from PUVA is converted into electrical energy and readout by instrument called radiometer. It is made up of a radiation filter, input optical and a detector where as that at specific wavelength known as the spectral radiation is measured with the much more complex spectroradiometer which includes a monochromator instead of filter. The radiation dose is then calculated as the product of measured irradiance and the exposure in time (Sec). Four commonly used are photomultiplier tube, vacuum photo tube, solid state photo diode, thermopile. Photo multiplier tube are very sensitive but fragile. Solid state photodiodes are more robust, small and suitable for rapid portable radiometry (eg) phototherapy equipments. Thermopile are

small robust, have flat spectral responses are best for the quick accurate measurements of monochoromatic irradiance or of serial broad band irradiance of fixed spectral content.

The dosimetry of photochemotherapy of vitiligo needs always to be done with special care because over exposure may result in serious adverse reactions. There are no parameters that allow a reliable prognosis for an individual patient. It has been demonstrated that after PUVA treatment, the majority of the patients retain PUVA induced repigmentation for many years. Neither the pathogenesis of vitiligo nor the mechanisms of regimentations by photo therapies are completely understood[3,18].

UV radiation is present in sunlight also. In vitiligo, 8-MOP is conjugated with sunlight exposure is called as PUVASOL therapy[2].

The exposure done is done in outdoor between 10 am to 3 pm, two or three times per week .It is never done on consecutive days. Sun exposure is initially limited to five or ten minutes for Type 1 / 2 or 3 and greater skin types respectively, increasing by five minutes with each exposure. At that time a gradual increase is allowed based on redness and tenderness for upto two hours[45]. The disadvantage of therapy is difficulty in quantifying UV rays and total amount of UV rays may also

vary according to the season, time of the day, latitude and condition of atmosphere[7].

The irradiation of light is measured in milliwatt/cm2 with the help of an approximately calibrated radiometer .The dose of UVA irradiation is employed to calculate the exposure time for the desired dose in Joules.

Energy (joule) = Power(watt) X exposure time (second)

Fluence (J/cm2 = irradiance (W/cm2) X exposure time (sec)

$$\text{Exposure time (mts)} = \frac{\text{Prescribed UVA dose (J/m2)}}{\text{0.06 irradiance (mw/cm2)}}$$

VARIATION OF IRRADIANCE.

Irradiance (power density) varies directly with power source and inversely with surface area (therefore inversely with the square of distance from the power source.

$11 \text{ X } D1^2 = 12 \text{ X } D2^2$ (I= irradiance; D= distance)

$D1^2 / T1 = D2^2 / T2$ (T= exposure time)

Grading of erythema

E0 - No erythema

E1 - Minimally perceptible erythema (faint pink)

E2 - Marked erythema (red)

E3 - Fiery red erythema with oedema

E4 - Fiery red erythema with oedema and blistering

In pigmented patient, sometimes erythema and oedema may not be seen. Instead of these, patient may complain of hotness and tightness of skin.

Erythema is a limiting factor in phototherapy – E1 should not be exceeded. The onset of UVA – induced erythema has a delayed onset of 48 hours after exposure.

MPD (Minimal phototoxic dose) = The dose of PUVA required to produce a E1 reaction 48 hours after exposure.

MED (Minimal erythemogenic dose) = The dose of UVB required to produce a E1 reaction 24 hours after exposure[13].

MPD is can be accomplished by using a template with six to eight 2 x 2 cm squares cut out and applied to a sun protected area, such as the buttocks. After the rest of the patient's skin is shielded with appropriate UV opaque covering, graduated doses of UV light can be delivered to the test site by sequentially blocking the template openings with opaque material at increments designed to produce an array of UV light exposure lightly less or greater than the expected MED or minimal phototoxic dose based on the patient history. This is done after administering the photosensitizer (1½ - 2 hrs) after oral psoralen and 1 hour after topical psoralen[5].

Usually the first dose range from 0.5 to 5 J /cm2. Minimum Phototoxic. Dose (MPD) thus determined indicates the first therapeutic UVA dose for the follow up and adjustment of the dose, determination of photosensitivity, pigment index (PDI) become necessary. This is done by reading the erythema and pigmentary reaction after 72 hours and 120 hours in the first test field exposed for MPD determination. The PDI serves to assess the patient's capacity to develop the tolerance to photo toxic reaction by pigmentary reaction of the skin[18,3].

Perifollicular pigmentary dots were the first to appear followed by the hyperpigmentation of the border. Dots of pigmentation usually

develop after 20 to 30 exposures. , 50 exposures on trunk and proximal extremities, and near total repigmentation usually requires 50 to 300 exposures[8].

VARIOUS SCALES IN PUVA ASSESSMENT

1) Based on RULE OF NINE[39]

2) Assessment scale proposed by Hossain[17]

Parameter	--	+	++	+++	++++
Change in colour	No change	Yellowish tint	Slight contrast between lesion color and surrounding skin colour	No contrast between lesion color and surrounding skin colour	100% remission in all treated lesions
Change in size	NO change	Up to 5mm reduction in diameter	Up to 10mm reduction in diameter	More than 10mm reduction in diameter	
Folliculocentric repigmentation	No repigmentation.	Upto 5mm perifollicular repigmentation	Upto 10mm perifollicular repigmentation	More than 10mm perifollicular repigmentation.	

3) Vitiligo Area Severity Index[69]

The percentage of vitiligo involvement is calculated in terms of hand units. One hand unit (which encompasses the palm plus the volar surface of all digits) is approximately equivalent to 1% of the total body surface area. The degree of pigmentation is estimated to the nearest of one of the following percentages : 100% - complete depigmentation, no pigment is present; 90% - specks of pigment present; 75%- depigmented area exceeds the pigmented area; 50%- pigmented and depigmented area

are equal; 25% - pigmented area exceed depigmented area; and 10% - only specks of depigmentation present.

The VASI for each body region is determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit measured patch. Total body VASI =Σ all body sites (Hand Units0 x (Residual depigmentation) Vitiligo disease activity score (VIDA). The VIDA is a six-point scale for assessing vitiligo activity. Scoring is based on the individual's own opinion of the present disease activity over time. Active vitiligo involves either expansion of existing lesions or appearance of new lesions. Grading is as follows : VIDA score +4- activity of 6 weeks or less duration : +3 – activity of 6 weeks to 3 months; +2- activity of 3-6 months ; +1- activity of 6-12 months; 0 – stable for 1 year or more; and – 1- stable with spontaneous repigmentation since 1 year or more. A low VIA score indicates less activity.

ADVANTAGE OF SYSTEMIC PUVA OVER TOPICAL PUVA:-

- Oral PUVA treatment is less laborious and time consuming than topical PUVA.
- Erythema and blister formation is less commonly seen than topical PUVA.

- Improvement is more regular than with topical PUVA[39].

PUVA and HIV Infection

Systemic PUVA can be safely used for the treatment of HIV positive infected patients and is a practical regimen with little or no risk of disease transmission and well accepted by the patients. But for more advanced HIV infection systemic PUVA is not recommended[47].

DISADVANTAGES :-

Systemic side effects such as nausea, vomiting, carcinogenic effects, and cataracts are more common with oral PUVA[21].

PUVA has been shown to effect immune reactions. PUVA also has possible effects on the function of polymorpho nuclear leucocytes, formation of antibodies, immune complexes and induction of auto immune diseases. PUVA treatment should be closely monitered for induction of LE[47].

INDICATION FOR PUVA IN VITILIGO

1. Generalized vitiligo (more than 20 % of body surface area)[46]
2. Segmental vitiligo
3. Acral vitiligo[14]

4. Acro facial vitiligo

5. No response to topical medication[3].

CONTRAINDICATION FOR PUVA IN VITILIGO

ABSOLUTE:-

1) Bloom's syndrome

2) Trichothiodystrophy.

3) Previous melanoma

4) Xeroderma pigmentosum.

5) Systemic lupus erythematosus.

6) Cockayne's syndrome

7) Gorlin′s syndrome[47]

RELATIVE CONTRAINDICATIONS:-[47]

MAJOR	MINOR
♦Age <10 years	•Age < 16 years
♦Concurrent Malignant disease	•Cataract
♦Concurrent Immuno Suppression	•Bullous Pemphigoid, pemphigus vulgaris
♦Pregnancy , Lactation	• Significant Hepatic dysfunction
♦Porphyria	Previous internal malignancy
♦Previous Exposure to arsenic and X rays	

SIDE EFFECTS OF PUVA[14,15,70,71,]

Acute clinical side effect :-

These are due to the drugs (photo toxic reactions)

1) Erythema
2) Pruritis
3) Koebnors Phenomenon
4) Severe pain in the skin
5) Drug eruptions
6) Nausea , headaches, bronchial hypersensitivity
7) Phyto photo dermatitis
8) Ankle edema
9) Blister.

DUE TO METHOXSALEN ALONE :-

Gastro intestinal disturbance, CNS disturbance like headache, dizziness, light headedness, depression, insomnia, feeling of detachment from the environment. Bronchoconstriction, hepatic toxicity and drug fever[71].

CHRONIC SIDE EFFECTS :-

- Hyper pigmentation and xerosis[14]
- Premature ageing and wrinkling[54]

- Hyper trichosis[2]
- Nail changes – pigmentation, subungual hemorrhage[43].
- Precancerous skin conditions – actinic keratosis[15], seborrhoeic keratosis , Keratoacanthoma , Bowen's disease[2].
- Cutaneous malignancy like squamous cell carcinoma, melanoma[36,48,65].
- Aggravation of underlying skin disease like seborrhoeic dermatitis, acne, bullous pemphigoid, lupus erythematosis, cataract, disseminated superficial actinic porokeratosis, hepatotoxicity, nephrotic syndrome and exacerbation of gouty arthritis[1,2].

COMBINATION OF TREATMENT UTILIZING PUVA :-

PUVA PLUS TOPICAL THERAPY

PUVA + Calcipotriene[70]

PUVA + Steroids

PUVA + Minoxidil

PUVA + Anapsos

PUVA +Autologous split skin graft[3] .

PUVA treatment can be divided into two phases ,

1. The clearing phase.
2. Maintenance phase.

The clearing phase begins with the commencement of therapy and ends with clearing of atleast 95 % of treatable lesions.

The maintenance phase on the other hand is subject to considerable variations in frequency and duration as well as dose adjustment.

The determination of the starting UVA dose has been classically dependant on the establishment of skin type in the United States and whereas in Europe, it is based on minimal phototoxic dose (MPD) and in some instances the photopigmentary index of each individual (PPI) .The Austrians use MPD or the combination of MPD and photoPigementary index[18].

FITZPATRICK SKIN TYPE[21]

Code	Description
I	Always burn , never tans
II	Always burn , tans minimally
III	Burn moderately, tan gradually and uniformly (light brown)
IV	Burn minimally , always tan well (moderate brown)
V	Rarely burns , tans profusely (dark brown)
VI	Never burns , deeply pigmented (black)

UVA Exposure according to Skin Type

Recommended Skin Type	Initial Maintenace	Dose (J/cm^2)	Increment dose (J/cm^2)
1	4-6	0.5-1	2.5-5
2	6-8	1-2	0.5
3	8-10	1.5-3	0.5-1
4	10-12	2-4	1
5	12-14	2.5-5	1
6	14-16	3-6	1-1.5

The dose of UVA is increased from 0.5 –1 J /cm2 depending on the skin type or an individual response. The treatment is given usually two to three times weekly atleast 48 hours apart to permit evaluation of any erythema resulting from preceding treatment. If painful eythema and blister persist and wide spread, the treatment should be restarted, once the lesion completely subsides and restarted at minimal dose lower than the previous treatment dose. If still erythema occurs, artificial UVA dose or sunlight exposure should be withheld constantly. Marked erythema due to photo toxicity should be avoided since subsequent koebnerization may cause reversal of repigmentation .

During the UVA irradiation, protective eye goggles should be worn. Clothing should not be worn and sun screen should not be used before UVL exposure. During UVL treatment, protection of face with a pillow case and male genitals with an athletic support is often advised. The patient should be advised to avoid exposure to sunlight for 8 hours

after taking UV light treatment. If exposure is unavoidable skin should be protected by clothing, hat, and sunscreens that block UVA[18,24].

Maintenance schedule

The final clearance dose of irradiation is held constant and the frequency of treatment is gradually reduced as follows.

Four treatments at weekly interval

Then,

Four treatments every other week

Then,

Four treatments every third week

Then,

Four treatments every fourth week

Then ,

Stop treatment or continue monthly treatment[70]

Special glasses should be worn to protect the eyes even when indoors; window glasses may not shield UVA light. Hence protective eyewear must be worn, lubricating lotion / Emollient lotions can be used for dry skin following the treatment[18].

If regimentation is not seen even after 20 – 30 treatments, the dose of 8 MOP can be increased. If still desired results are not achieved

after another 20 – 30 treatments, the treatment is to be viewed as a failure[13].

If treatment is interrupted before an area gets completely repigmented, the area once again becomes depigmented within a short time . Psoralen therapy also increase the tolerance of affected skin to sunlight possibly through thickening of the stratum corneum[3].

TOPICAL PUVA.

If vitiligo macule is less than 6 cm2 in size, 0.1 % of psoralen lotion can be applied weekly followed by one and half to two hours later exposed to sunlight for 30 – 60 seconds. And duration can be increased by 30 seconds per sitting until light erythema occurs on the day following the exposure. Alternatively the area is exposed to black light source at a distance of 4 cm for 4-5 minutes. Initial exposure dose is 0.5 J/cm2, with increment of 0.25 –0.7 J/cm2 in the subsequent treatment until a light pink colour is obtained. After treatment exposure, the area should be washed with soap and water and covered with a clothing or with a sunscreen[3,18].

Other modalities available are :-

- Bath PUVA and Bath suit PUVA. The advantage of this method is systemic toxicity can be avoided[18].
- 5- MOP (5 Methoxy Psoralen)

A dose of 1.2 –1.8 mg /Kg body weight is said to be as effective as 8- MOP when given at a higher dose or a high dose of UVA radiation . Side effects are less and decreased phototoxicity due to decreased concentration in the epidermis[2,34].

- Trimethyl Psoralen (4, 5, 8 MOP) is often used topically and orally[21].
- 3 Carbethoxy Psoralen (3 CP) may be therapeutically effective but less phototoxic than 8 MOP in humans[18].

METHODS AND MATERIALS

Forty one patients of either sex with stable generalized type, acral, acrofacial type of vitiligo with > 20 % of body surface area involvement were enrolled for the study after obtaining the informed consent. History included the following:

1. Age of onset of depigmentation
2. Course of the disease – stability, rate of progression
3. Potential precipitating events including emotional stress, cutaneous trauma
4. Any history of photosensitivity
5. Ocular or auditory dysfunction
6. Family history of vitiligo and early graying of hair
7. Personal or family history of autoimmune diseases

All patients were examined under good light. Importance for the distribution, number of lesions, colour of lesions, the affected sites in the skin,approximate surface area of depigmentation, pattern of vitiligo and mucosal involvement were taken into account. Any presence of leukotrichia in the patch were noted.

Any associated autoimmune disorders if present were noted . Laboratory investigations like routine blood examination (Hb, TC, DC, ESR), urine analysis, liver function tests, thyroid profile were done.

Blood group, peripheral smears, blood sugar, serum creatinine were also done .

INDICATIONS OF PUVA –INCLUSION CRITERIA

1) Generalized stable vitiligo
2) Acro facial vitiligo
3) Acral vitiligo
4) Patient who has given consent for clinical photo and treatment

EXCLUSION CRITERIA

1. Patient not willing to give written consent
2. Patient below 12 years and above 60 years
3. History of photo sensitivity and photo sensitive skin disorders
4. Pregnancy and lactation
5. Concurrent immuno suppressive and premalignant skin disease
6. Significant hepatic and renal dysfunction

Audiograms were done to rule out any sensory neural deafness. Fundoscopy was done to rule out cataract and retinal pathology .Clinical photographs were taken for all the patients before and after exposure to PUVA therapy. This study was randomized single blinded age and sex matched.

In each case initial lesions on both sides of the body were assessed with the **Rule of Nine.** 8 -MOP tablets were given according

to the weight of the patient .After one and half to two hours the patients were subjected to UVA exposure artificial phototherapy chamber starting with a dose of 4 J /m2 over whole body.

An increase of dosage by 0.5J/cm2 was done provided there was no generalized erythema or other side effects. Comparative assessment of index lesions was done on each side in each case before starting treatment and after every five exposure to UVA treatment for a period of 8 – 10 months..

METHODOLOGY

8 MOP tablets are given in the following doses (which is equal to 0.4 – 0.6mg./ kg body wt.)

Patient's Weight (Kg)	**Dose in Mg. (1 tab – 10 mg)[70]**
> 30	10
30-60	20
65-90	30
> 90	40

Drugs was taken in the empty stomach because of its absorption was enhanced. If patient complained of nausea the tablets were taken after a small meal. Subsequently after 1 ½ -2 Hrs, the patient's whole body was irradiated with UVA by an appropriate irradiation system. The

starting dose (Joule) was determined by Fitzpatrick skin typing. As the Indians belong to Fitzpatrick's Skin typing V, started at 4J/Sq.cm[70].

Repeated exposure for 2 times/week was done to clear PUVA responsive disease. Increment dose of 0.5 joules/sq.cm/1-2week during each exposure was based on the patient's response[14].

During treatment the eyes were protected by wearing UV – blocking goggles. An occasional exception was made in patients with recalcitrant disease of the eyelids or periorbital skin, and at the physician's discretion[40].

Before and after treatment with photochemotherapy, a) Patients were advised to wear UVA – blocking glasses, whenever using sunlight for illumination, from the time of exposure to psoralen until sunset that day. In addition, patients were encouraged to wear UV – blocking glasses when exposed to sunlight on the following day.

Patients were advised to should avoid unnecessary exposure to sunlight on days they, receive treatment and were discouraged from deliberate exposure to sunlight on nontreatment days. Patients were encouraged to use sunscreen on exposed areas.

When trace of erythema was seen after 72 hrs, dose was not increased and patients were treated with previous exposure time if side

effects were noted. When more than 95% clearance was obtained, the last dosage was maintained and maintenance schedule was given. The patients were assessed every fortnightly and values tabulated.

RESULTS

TABLE 1

OVERALL RESPONSE RATE

Data	Mean	SD	Minimum	Maximum
Age	41.27	11.45	18	60
No .of patch	27.73	8.58	15	50
No. of month	94.07	66.62	12	240
Extent of lesion	31.05	10.27	15	60
% of area involved	34.03	11.02	15	60
No.of sitting	57.67	30.67	5	100
Last visit	19.17	7	10	35

TABLE 2

TYPE OF VITILIGO

Type	Total patient	Percentage
Generalized	20	66.7 %
Acral	5	16.6%
Acro facial	5	16.6%

TABLE 3

AGE RESPONSE TO PUVA

Age (yrs)	Generalised type-Vitiligo Vulgaris			Acral			Acro Facial		
	M	F	Response	M	F	%	M	F	%
10-20	--	1	75	--	--	--	1	--	58
21-30	2	--	63.5	2	1	43.6	--	1	11
31-40	1	5	44	--	1	50	--	--	--
41-50	3	3	36.7	--	--	--	3	--	42.6
51-60	4	1	57.45	1	--	25	--	--	--

Overall response	Vitiligo Vulgaris	Acral	Acrofacial
Female	50.7 %	50.00 %	11.1 %
Male	60.6 %	33.33 %	46.5 %

TABLE 4

ACUTE SIDE EFFECTS

a) Generalized type of Vitiligo

Symptoms	No. of Patients (20)	%
Pruritus	8	26.6
Erythema	10	33.3
Bulla	2	6.66
Xerosis	7	23.33

b) Acral

Symptoms	No. of Patients (5)	%
Pruritus	1	3.3
Erythema	1	3.3
Bulla	0	-
Xerosis	1	3.3

c) Acrofacial

Symptoms	No. of Patients (5)	%
Pruritus	1	3.3
Erythemia	1	3.3
Bulla	1	3.3
Xerosis	1	3.3

TABLE 5

EXACERBATION FACTORS IN RELATION TO PUVA

	Mild	Moderate	Good	Excellent
Normal (24)	7	6	4	7
Exacerbation (6)	1	0	1	4

X^2 = 3.6 p = 0.31 NIL SIGNIFICANT

TABLE 6

RELATION OF PHYSICAL AND CHEMICAL INJURY TO PUVA

	Mild	Moderate	Good	Excellent
Normal	8	4	4	11
INJURY	0	2	1	0

X^2 = 6.3 p = 0.09 NIL SIGNIFICANT

Causes of early discontinuation of PUVA in this study :

1)	Long Distance	4
2)	Lack of Compliance	3
3)	Fear of side effects	2
4)	Associated with DM and hypertension	2
	Total	**11**

TABLE - 7

FAMILY HISTORY AND PUVA RESPONSE

	Mild	Moderate	Good	Excellent
Nil	3	5	3	7
Consanguinous marriage	2	0	1	2
Family members	3	1	1	2

X^2 = 3.11 p = 0.38 NIL SIGNIFICANT

TABLE – 8

OVERALL RESPONSE IN VARIOUS TYPES OF VITILIGO

Type	Mild (<25 %)	Moderate (25-50 %)	Good (50- 75 %)	Excellent (> 75 %)
Generalized (20)	2	6	9	3
Acral (5)	1	2	2	--
Acrofacial (5)	1	3	1	--

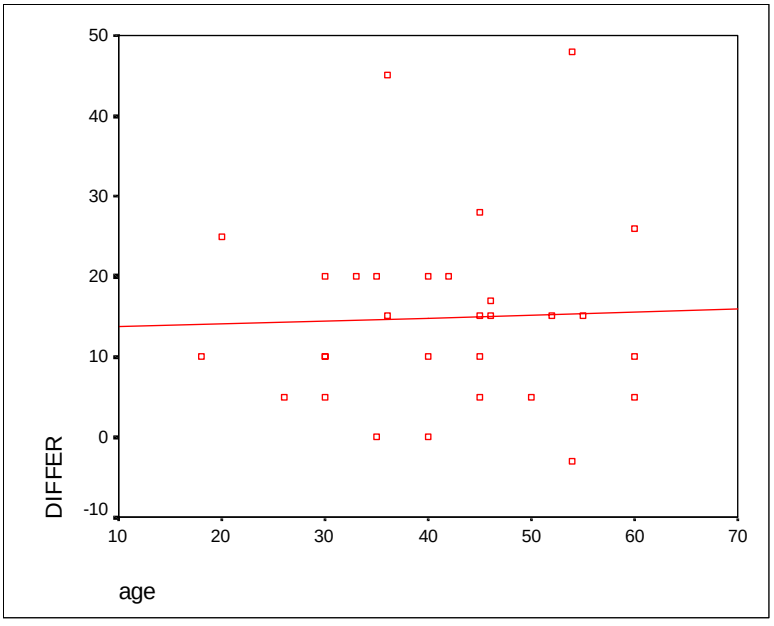
TABLE – 9

PAIRED SAMPLES STATISTICS

	N	Mean	SD	Paired t-test
Initially involved	30	34.03	11.022	t = 6.99
Last visit	30	19.17	6.998	p = 0.001

(P < 0.05)

AGE RESPONSE IN RELATION TO PUVA



Nil Significant

DISCUSSION

Vitligo is a disease of unknown aetiology. Though it is not a life threatening disease and does not require treatment, it causes cosmetic disfigurement, emotional stress and social stigma. Therapeutic approaches are directed to reverse the progressive loss of pigment producing epidermal melanocytes and to reconstitute the normal skin colour. Upto 20% patients with vitiligo experience transient repigmentation in some skin area upon exposure to sunlight. However photochemotherapy can induce permanent cosmetically acceptable result[9].

Aim of our study is to evaluate efficacy of PUVA treatment in South Indian vitiligo patients by this prospective study. Forty one patients were enrolled for this study. Out of which thirty patients regularly took PUVA therapy. (<25% of their scheduled PUVA therapy)

The age of these patients ranged from 18 to 60 yrs. (mean age 41.72+/- 11.44)

Sixteen male patients and fourteen female patients were taken up for this study giving male to female ratio of 1.2:1. Family history of vitiligo was found in seven patients (23.33%) of which two were acral type (1 acral, 1 acrofacial type) and five were generalized type.

The types of vitiligo taken in our study were generalized (20 patients, 66.7%) , acral in five patients (16.6%) acrofacial in 5 patients (16.6%). Duration of the disease ranged from 12 months to 240 months (mean 94.07+/- 66.62). The percentage of the area of vitiligenous patches extended from 15% to 60% giving a mean of 34.03% +/- 11.02%.

The cumulative doses ranged from 20 J/cm2 to 440 J /cm 2 with a mean of 230.4 J/cm^2. Number of sessions to initiate repigmentation ranged from 6 to 15 sessions (8.45%) in case of generalized type and in case of acral and acrofacial type 8 to 18 sessions (11%) which is comparable to the study done by James E.Fluton where clinical repigmentation started after two to ten treatments in generalized type of vitiligo[30].

Onset of repigmentation was found to be earlier in young males in generalized type and in young females in case of acral type. In acrofacial type it was seen in young male patients[59].

The maintenance doses ranged from 6 to 12 J/cm^2 giving a mean of 6.77J/cm2. When the maximum cumulative doses of 440J/cm^2 (100 exposures) was given, good response was noticed among the younger age groups in all three types of vitiligo. (acral, acrofacial and generalized types)[59].

On following up the patients fort-nightly, initial erythema was noticed in 40% of patients followed by perifollicular repigmentation, which is consistent with the study stating that initial erythema was necessary for repigmentation[8]. (Fig. 1 & 2)

All the patients were assessed based on the "Rule of Nine". In our study we noticed along with perifollicular pigmentation hyperpigmentation at the border of the patches as reported earlier[24,2].

In generalized type, excellent response was seen in 3 patients (15%), good response in 9 patients (45%), moderate response in 6 patients (30%) and mild response in 2 patients (20%). (Fig.3, 4,5,6,7,8,9 & 10)

In acral type good response was seen in two patients (40%)., moderate response was seen in two patients (40%) and mild response in 1 patient(20%). (Fig. 11,12,13 & 14).

In acrofacial type good response was seen in 1 patient (20%) , moderate response in 3 patients (60%) and mild response in 1 patient (20%)

Our study showed that analysis of factors affecting the response rate such as age, koebnerisation, exacerbating factors like sunlight, emotion, stress, infection etc., do not affect response rate which also correlate the previous studies[68].

In our study , good response was found in the patients with blood group "O" positive but Srivastava and Shukla observed more predilection for the blood group "B" and "AB"[22].

Acute side effects noticed in our study were erythema, pruritus, xerosis and bulla. In generalized type, pruritus was seen in eight patients (26.6%), erythema in 10 patients (33.3%) bullae in 2 patients (6.66%) and xerosis in 7 patients (23.33%). In acral type pruritus , xerosis and erythema was observed in one patient each (3.3%). In acrofacial type of vitiligo pruritus, xerosis, erythema and bullae were noticed in 1 patient each (3.3%).

The mild erythema (grade 1)[13] was observed after 12 to 24 hrs. and subsided by 42 to 72 hrs. is compatible with previous studies, grading as per previous reference[2].

We found that none of the patients enrolled in the study developed pain and painful erythema over the vitiliginous patches after 80 to 100 sessions. Erythema was treated with cool compresses, emollient lotions and shielding of affected area. Pruritus was treated with oral anti histamine,emollient and topical steroids . Bulla was noticed in two patients in case of generalized type of vitiligo at $6J/cm^2$.The treatment was restarted after the lesions had completely healed at a dose lower than the previous treatment dose ($2J/cm^2$). After 10 exposures of PUVA, 2 patients again developed blister and therefore were discontinued. Bulla was observed in 1 patient in acrofacial type at 10J/cm2. Hence, the patient was placed in the maintenance dose of 8J/Sq.cm[13].

Chronic side effects like hypertrichosis was seen in one patient of generalized type of vitiligo over the patch and other long term side effects like cataract, premature aging and PUVA lentigenes were not observed in study[67]. Similar to the previous study done in the UVA response in the vitiligo in Saudi patients.

At the end of our study (8-10 months) bio chemical parameters were again repeated. None of the patients showed any significant changes in their blood parameters.

In our study, trunk, face, arms, legs showed near complete repigmentation, while distal dorsal surface of hands, feet, tips of fingers, palms and soles , nipples bony prominences rarely showed complete repigmentation, which is consistent with the previous study of PUVA in Saudi vitiligo patients[4]. The patches with leukotrichia showed poor repigmentation[21].

CONCLUSION

- In our study, the only factor to affect the overall response rate with the statistical significance (P.001) was the surface area of involvement was directly proportional to the total session to induce pigmentation (p value <0.05).
- Our data showed that the following factors like the age of the patient, family History of vitiligo, Koebnerization, precipitating factors and the age at the onset of disease have no influence on repigmentaion, though the onset of repigmentation was found to be earlier in younger patients.
- Hairy areas (Face, Legs, arms, trunk) were more sensitive to therapy while non hairy areas (mucosa, finger tips, toe tips, palms & soles) were less sensitive to therapy.
- Generalized type was the best type to respond very well. Acral and acrofacial types were resistant to therapy.
- Good response was noticed in young patients with blood group 'O' positive individuals.
- In our study, patients with longer duration of disease showed slower response to therapy.
- We conclude, that Puva is effective, safe and cosmetically acceptable therapy for vitiligo.

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PROFORMA

Name : Age :

Address : Sex :

Occupation :

1) Complaints : No. of patches, Sites

2) Durations :

3) Activity : Progressive, Static, Spontaneous repigmentation

4) Factors exacerbating - seasonal, emotional, infections, drugs, sunlight

5) History of Injury - Physical - present / absence

Chemical - present / absence

6) Associated Visual disturbance / Deafness

7) Family History - Consangunity in parents
Other family members affected with Vitiligo
Associated diseases in the family

8) Treatment History - Ayurvedic
Homeopathic
Allopathic
No treatment

9) Associated autoimmune diseases :

1) Hypothyroidisrn

2) Hyper thyroidism

3) Pernicious anaemia

4) Diabetic mollitus

5) Rheumatoid arthritis

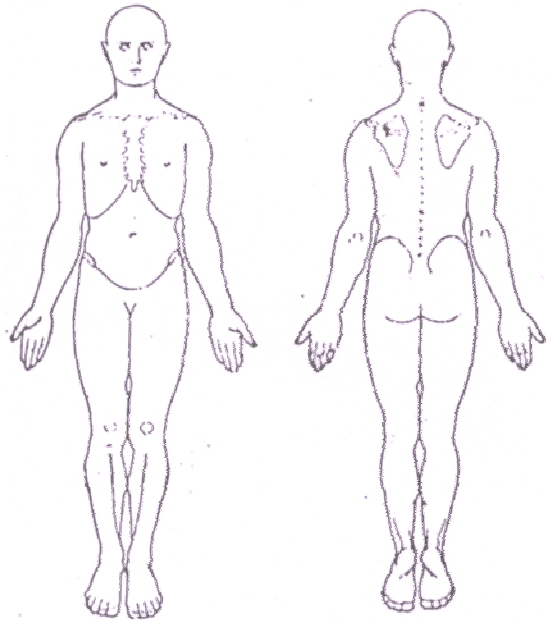
6} Alopecia areata

7) Addisons disease

0) Atopic Dormntilis

10) Examination (sites;
Sun exposed
Covered area
mucosa - oral, genital, scalp
palm / sole
leucotrichia
Loebner's phenomenon

11)



12) Extent (%)

type of vitiligo	Local	Generalised
	Focal	vitiligo vulgaris
	mucosal	Acrofacial
	segmental	universalis

Whole body / Hand + Foot

14) PUVA
15) General Examination
Anaemia
Jaundice
cyanosis
clubbing
Lymphadenopathy

16) Systemic Examination : CVS :

RS :

Abdomen :

17) Particulars :

Date of Visit

Weight

Height

Pulse Rate

Blood Pressure

16) Investigations :

1) Hb								
2) TC								
3) DC								
4) ESR								
5) Peripheral Smear								
6) Blood grouping								
7) Blood Sugar								
8) Blood Urea								
9) Serum Creatinine								
10) Liver Functin Test								
SGOT								
SGPT								
Alkaline phosphatase								
Total bilirubin								

19) Psoralen Dose : Oral / topical application

20)

Date of Visit	Dose f UVA	Side effects	New Lesions	Old Lesions			Repigmentation
				Stat	Worsen	Better	

ABBREVIATIONS

TGF	-	Transfer Growth Factor
IR	-	Infrared Radiation
IL6	-	Interleukin
UVA	-	Ultraviolet A Rays
UVB	-	Ultraviolet B Rays
UVC	-	Ultraviolet C Rays
DM	-	Diabetes Mellitus
CLA	-	Cutaneous Lymphocytic Antigen

PUVA CHAMBER

BEFORE ILLUMINATION

AFTER ILLUMINATION

HAND AND FOOT PUVA

GENERALISED TYPE OF VITILIGO VULGARIS

BEFORE PUVA (Fig. 3)

AFTER PUVA (Fig. 4)

GENERALISED TYPE OF VITILIGO VULGARIS

BEFORE PUVA (Fig. 7)

AFTER PUVA (Fig. 8)

GENERALISED TYPE OF VITILIGO VULGARIS

BEFORE PUVA (Fig. 5)

AFTER PUVA (Fig. 6)

GENERALISED TYPE OF VITILIGO VULGARIS

BEFORE PUVA (Fig. 9)

AFTER PUVA (Fig. 10)

GENERALISED TYPE OF VITILIGO VULGARIS

BEFORE PUVA (Fig. 1)

AFTER PUVA (Fig. 2)

ACRAL TYPE OF VITILIGO

BEFORE TREATMENT (Fig. 11)

AFTER TREATMENT (Fig. 12)

COMPLICATION

ERYTHEMA

BLISTER

RUPTURE BULLA

EROSION AND ULCER

ACRAL TYPE OF VITILIGO

BEFORE PUVA (Fig. 13)

AFTER PUVA (Fig. 14)